5. Analysis Plan - The Analysis Plan, which can be a separate document, should describe all important analyses in sufficient detail that a statistician given the Analysis Plan and the data, would arrive at the same results as the sponsor's analyses. Each proposed statistical method should be described/identified including which computer software is to be used.

6. Sample Size Calculations: When calculating sample size, a significance level of 95% (two-tailed) and a power level of 80% -90% are generally considered acceptable. If the correlation of shocks within patients are adequately accounted for and a correlated analysis is planned, sample size may be based on shocks, otherwise the experimental unit should be the patient.

The two-tailed p-value $p < 0.05$ is an arbitrary (but not capricious) choice. It simply "sets the standard" at 1 chance in 20 that this result was due to chance alone. A p (1 tailed) < 0.05 is equivalent to a p (2 tailed) < 0.10 and "lowers the standard" to 1 chance in 10 that this result was due to chance alone.

Where efficacy is to be shown, sample size calculations will be based on the expected and comparison primary endpoints. The sample size and center requirements proposed by the sponsor will be reviewed on a case by case basis.

Investigator Qualifications - Investigators for ICD studies should be scientifically qualified and clinically competent medical persons selected based upon training and/or experience with similar devices.

7. Patient Access Considerations - While important, statistical determination of study sample size is only one of the considerations in the determination of the number of patients and number of institutions involved in pre-approval ICD development. Other considerations include:

1. Including a large number centers provides more rapid enrollment, clinical exposure to a greater mix of investigators, and more diverse patient demographics. A smaller number of centers (more patients per center) permits better assessment of the learning effect and a greater opportunity to assess center differences (center effect).

2. When results of clinical studies appear to satisfy safety and efficacy concerns, every effort will be made to continue patient access to the ICD during the review and approval process.

3. The agency is also aware of the economic stress on manufacturers from the interruption of ICD distribution between the completion of clinical studies and PMA approval. The agency is committed to minimizing this stress. The most important element in minimizing this interruption is communication (early, frequent, and honest) between the sponsor and the review team.

8. Data Management - The protocol should describe how data integrity will be maintained. This includes case report forms (CRF's) appropriate to the outcomes which gather the necessary safety and effectiveness data, competent clinical monitoring which identify problems early and maintain completeness and high data reliability, data entry with tracking of changes, and submission of data in a usable format.

9. Risk Analysis - Adequately demonstrate that the benefit and knowledge to be gained outweigh the risk to the subjects, by addressing the following:

1 - Minimize Risks - Describe how the risk to the subject will be minimized over the course of the trial. As examples, these can include the clearly defined inclusion criteria which ensure only properly selected patients will be enrolled, and that patient treatment and follow-up are consistent with established therapies for the same medical condition.

2 - Use Without Adverse Effects - Summarize any available data that supports the use of the device without any unacceptable adverse effects. Data from outside the US (OUS) data are acceptable if they are collected in accord with the Declaration of Helsinki [26], identical protocol and devices were used, the collection of follow up data was complete, and the practice of medicine is similar to these practices in the US.

Appendix B. Clinical Data Requirements

When developing the clinical data to support the safety, effectiveness, and labeling of an ICD, the applicant should take note of the following:

1. Patient Population (indications) - Data should be reported by patient groups:

- Ventricular Fibrillation (VF), spontaneous or induced
- Ventricular Tachycardia (VT), spontaneous or induced
- VT/VF, spontaneous or induced

2. Reporting and/or Follow-up Intervals - Reported data for the following specific times:

- Pre implant (pre-operative)
- Implant
- Predischarge (optional)
- Follow-up at 1 month (optional) then every 3-4 months or as clinically indicated

3. Lead Systems and Delivery - The lead system and delivery of treatment can be specified in certain data if pertinent. The following information may be collected:

- Lead configuration
- Waveform

4. Data Collection Definitions - ICD evaluation should include the patient data as summarized below:

Pre implant

- patient history
- inducibility (EP testing)
- VF or VT
- MVT, PVT/VF, hemodynamically stable or unstable
- return of rhythm after induction (may be bradycardia or normal sinus rhythm)
- drug therapy evaluation)

Implant

- DFT (defibrillation threshold, the minimum energy required for consistent defibrillation): used to estimate the safety margin for defibrillation [28-50]
- LED (lowest energy of defibrillation): needed when thresholds were not established because a patient was not tested to a failed level.
- drugs: pre implant and ongoing drug therapy at implant (drug history is noted and drug study is not attempted).
- patients not meeting implant criteria: report number of patients and the resultant protocol deviation for each.
- lead impedance: pace/sense impedance; for defibrillator leads, mean is reported rather than each patient's measurement. Maximum, minimum, and standard deviation required.
- pacing: pace/sense data; for epicardial or endocardial leads, the pre-shock, post-shock, and pacing threshold evaluations are required (anti-tachy pacing may or may not be evaluated at implant)
- defibrillation: sensing data, P/T wave testing (oversensing is the concern).
- concomitant surgery: data pertaining to necessary surgical interventions, bypass, etc.
- surgical approach for each case: median sternotomy, lateral thoracotomy, sub xyphoid, and transvenous.

Follow-up Data: should include observations that involve electrophysiological or hemodynamic changes following therapy and not collected as a part of adverse events. Exact date of each major event, especially death, should be reported whenever possible.

- DFT: may not be obtained on every patient, however, encouraged at EP testing if there have been no spontaneous events since implant/predischarge
- LED testing: usually measured at EP study
- Spontaneous episodes: VT episodes - report number of ATP, cardioversions or defibrillation shocks, VF episodes - report number of defibrillation shocks, and death
- Induced events: report the number of induced VT and VF episodes
- Adverse events: report the number and describe in detail any observations or complications and subsequent resolution

  Observation is defined as an adverse events which is correctable by noninvasive measures.

  Complication is defined as an adverse event requiring invasive measures to correct.
- Survival rates: survival rates compared to ICD population
- Report all deaths: use the following categories - total mortality, total cardiac death, sudden cardiac death, non- sudden cardiac death and non-cardiac death (see Appendix E for definitions)

5. Records Requirements

The patient population should be described with such demographic factors as age, sex, indications, associated conditions, symptoms, concomitant drug therapy, and duration of implant. There should be a list of investigators and institutions, as well as the number of devices implanted by them.

Deviations from the clinical protocol or data collection methods should be fully documented and, if appropriate, reported and explained to the FDA in an IDE/PMA supplement/amendment.

Note: It is recognized reporting requirements will depend on the particular endpoints and study design.

Appendix C. Reporting of the Clinical Trial

Reporting of the clinical data to support the safety, effectiveness, and labeling of an ICD should include the following:

1. Reporting and Analysis by Treatment Group - The following information may be presented in the form of histograms, charts, tables, etc.:

- Patient demographics, clinical history, EP study findings
- Safety data including mortality and adverse events
- The conversion effectiveness of induced/spontaneous episodes of ventricular tachyarrhythmias and bradycardia that have been successfully treated by the system with the available modes of therapy
- Data evaluating long-term performance of sensing and defibrillation leads. Generally accepted time to chronicity is 3-6 months post implantation.
- Data regarding all inappropriate device responses.
  - adherence to protocol;
- Data which support adequate clinical experience in the use of device accessories, e.g., external tester (fibrillation induction, Non-Invasive Programmable Stimulation (NIPS) function)
- Demonstration of device efficacy in the treatment of VF in those patients who were not induced at implant and who have not had spontaneous episodes of VF
  - all protocol deviations and violations
  - a justification for pooling the data when the study includes different device models.
- survival analysis
- complications and observations.

Note: The follow-up window for device testing at the different follow-up times can be specified in the protocol and/or analysis plan.

2. Reporting and Analysis at Implant/Follow-up - Should include:

- number of induced and spontaneous VT and VF episodes, VT and VF conversion efficacy;
- parameter settings for VF and VT;
- effectiveness data with use of each of the device's therapies and capabilities;
- DFT data and impedance measurements;
- cases of inappropriate sensing and shock delivery*;
- device activations (without delivered therapy) resulting in aborted shocks;
- the number of patients on antiarrhythmic drug therapy;
- complications and observations.
- complications-free survival
- cumulative survival from sudden cardiac death and death from all causes

** Raviele, et al, defined inappropriate shocks as "associated with documented supraventricular tachyarrhythmias or sinus tachycardia, or those not preceded by specific symptoms" [50].*

3. Data Obtained Outside the-US - If clinical data are obtained from one or more centers outside the-US (OUS) as a part of an IDE approved protocol, then the data should be evaluated for poolability and handled as with any other study center.

For data obtained from OUS centers not under an IDE intended to support safety and effectiveness in the PMA, a separate presentation (as described in the sections above) may be provided.

4. Evaluation of Longevity - Longevity models and predictions based on the clinical experience might include:

- A discussion of and an analysis of the data which support battery life information (end-of-life (EOL) and elective replacement indicator (ERI)) taking into account charging, pacing/sensing and the delivery of therapies
- A summary of the clinical experience which supports device longevity predictions. For example, in those patients who have had the device for up to 2 years (how were these patients programmed, number of device activations and shocks delivered for the various therapies (inductions and spontaneous treatments)
- Sterility and shelf life information for the system (pulse generator and all sterile components) should be provided.

5. Report of Lead Function - The leads should be tested at implant (the manufacturer's implant criteria may vary), chronic follow-up and periodically to determine proper functioning. Measurements and/or tests such as the induction of the patient's arrhythmia, DFT or lowest energy to defibrillate (LED) tests, amplitude, pacing and defibrillation lead impedance and x-rays or fluoroscopy are done to verify placement and performance. The following information should be included in the report of the clinical trial for both nonthoracotomay and epicardial leads:

- a comparison of the clinical experience and performance of the leads to the experience of a marketed epicardial and/or non-thoracotomy lead system;
- a breakdown of the implant configurations and the conversion effectiveness of each configuration;
- a discussion of all protocol deviations and follow-up data on all patients who did not meet the implant criteria and who did not have the recommended 10 Joule safety margin;
- recommendations for lead configuration testing;

- how clinical experience, including success and survival by primary arrhythmia, has been used to identify patients who are candidates for the nonthoracotomy lead system

6. Adverse Events (Complications and Observations) - The following should be addressed regarding complications and observations:

Observation is defined as an adverse events which is correctable by noninvasive measures, e.g., reprogramming for loss of capture for pacing, new arrhythmia morphology following therapy, fibrillation induction by inappropriate shock, elevated DFT, transient failure to sense electrograms or antibiotic treatment of pocket infection.

Complication is defined as an adverse event requiring invasive measures to correct, e.g., surgical evacuation of a hematoma, lead dislodgment requiring invasive lead repositioning, or generator replacement.

- specific definitions of a complication and observation for this study;
- report of all failure and complication rates associated with the system; and
- a statistical test for differences in the overall adverse event rate between the ICD under study and the control treatment

7. Survival Statistics - The study results and survival statistics should be stratified to take into account biases including:

- underlying disease;
- concomitant antiarrhythmic drug therapy; and
- an implantable pacemaker;.

The survival results should compare favorably with the historical control as specified in the original study hypotheses.

8. Mortality Rate/Deaths - Mortality information presented should include:

- clear definitions of patient death categories;
- overall mortality rate;
- operative mortality rate (perioperative deaths)
- number of deaths with the device programmed OFF/ON/BACKUP mode;
- documented patient deaths.

Appendix D. Required Postmarket Surveillance (RPS) Study Design

The headings below correspond to those used in "Draft Guidance to Manufacturers on the Development of Required Postmarket Surveillance Study Protocols under Section 522(a)(1) of the Federal Food, Drug, and Cosmetic Act."

Each manufacturer's Required Postmarket Surveillance (RPS) Study for ICDs have the following overall objectives:

a. To provide statistically **valid patient and device survival data** for generators and leads (grouped by technical and/or clinical applications) implanted in the general population under actual conditions of use;

b. Once a model for acceptable performance is generated and validated in the future by multiple manufacturers, to **provide an early warning system** for the identification of hardware and software failures in ICD systems implanted in the general population under actual conditions of use.

The headings below in curly brackets { }correspond to those used in "Draft Guidance to Manufacturers on the Development of Required Postmarket Surveillance Study Protocols [8].

1. Study Objectives {A. Study Objectives Specific to the Active Component}

CDRH recommends that each manufacturer's active study of Required Postmarket Surveillance for ICDs have the following objectives:

a. In a representative group of a few hundred patients, evaluate long term safety and effectiveness based on actuarially and numerically reported all-cause mortality rates, sudden cardiac death rates, perioperative mortality rates, generator complication rates, generator explant rates, lead complication/failure rates, and lead explant rates.

b. Provide information on battery longevity, and potential unintended inactivations, inappropriate shocks, and episodes of electromagnetic interference from environmental sources.

c. Once a model for acceptable performance is generated and validated in the future by multiple manufacturers, provide an early warning system regarding failures in ICDs implanted in a sample of patients representative of the general population under actual conditions of use.

Hypothesis: The 95% confidence limit of the clinical experience of patients implanted with the ICD models under study is statistically no worse than the average or standard clinical experience of patients implanted with other ICD models giving minimally acceptable performance (after adjustment for potentially confounding variables such as patient age, gender, clinical diagnosis, and baseline clinical condition). The clinical performance will be assessed by multiple variables such as all-cause mortality rates, sudden cardiac death rates, perioperative mortality rates, generator complication rates, generator explant rates, lead complication/failure rates, and lead explant rates.

2. Study Variables {B. Study Variables}

Baseline variables that could potentially confound the interpretation of study endpoint data include the following:

a. Indications for use -
   i. type of underlying arrhythmia as assessed in the electrophysiology laboratory.
   ii. previous sudden cardiac death experiences
b. Age
c. Gender
d. Left ventricular ejection fraction (LVEF)
e. New York Heart Association Classification
f. Ability to tolerate arrhythmia
g. Type of underlying heart disease
h. Taking concomitant medication
i. For generator recipients, type of concomitant ICD lead placement or other concomitant surgical procedure

Study endpoints regarding generators include the following:

a. All-cause mortality
b. Sudden cardiac death
c. Perioperative mortality
d. Overall complication rate
e. Episodes of inappropriate shock, unintended inactivation, EMI interference
f. Battery depletion
g. Explant rate
h. Proportion returned

Study endpoints regarding leads include the following:

a. All-cause mortality
b. Sudden cardiac death
c. Perioperative mortality
d. Overall complication/failure rate
e. Explant rate
f. Proportion returned

Denominator Data: {B1. Discussion of Denominator Data} The study population should consist of approximately three hundred patients implanted in the United States with any model listed in the original or supplemental PMA submissions. See the discussion of study size in section C2 and pooling in section C2b below.

3. Study Design/Type of Study {C. and C1. Study Design/Type of Study}

CDRH believes that an RPS for ICDs should be comprised of a clinically based study of a well-defined discrete group of a few hundred patients. This study (employing ACTIVE data collection techniques) would be intended to produce statistically significantly meaningful rates of generator explant, lead explant, lead failure/complication, device-aided patient survival, adverse events after generator implant such as complications, and qualitative information that might help identify the causes of device failures.

The major emphasis of a proposed study should be the generation of an actuarially (survival analysis) [9] derived all-cause mortality rate in a sample of approximately 300 patients. A manufacturer's RPS submissions should provide a brief summary of the complication/observation rates found in their Investigational Device Exemption (IDE) studies, as well as a summary of representative published studies in the scientific literature regarding the performance rates historically seen for other ICDs.

In addition, the manufacturer is encouraged to present a justification for any proposed grouping of models (see section below).

The agency will require the manufacturer to make a good faith effort to investigate and report using in situ interrogation and returned product analysis to analyze the ICDs of any patients who die.

Study Size: {C2. Study Size} The sample size should be sufficient to provide an early warning at 3 years if adverse event rates of 1% or greater under actual conditions of use are more than double what they are expected to be based on typical IDE or published scientific article results.

More specifically, for every model (or group of pooled models) to be newly studied under RPS, the agency requires a study size that will, at a minimum, be 90% likely to detect if there is more than a doubling in adverse event rates of 1% or more at 3 years. Use of a representative value for losses to follow-up, and an alpha level of 5% against the representative value would be appropriate.

As **an illustrative example** using the method of Peto et al.[10], to estimate a 1% failure rate to a precision of an additional 1% at 3 years, a sample size of ((Z**2)(0.99**2)(.01))/(0.01**2) = 266 patients would be required if none were lost to follow-up, and Z equals 1.645 for a one-sided test with an alpha of 0.05. Beta error is not accounted for in the estimation. If 60% follow-up at 3 years is expected, then 266/0.6 = 442 patients need to be enrolled.

When the total number of ICDs implanted is small, the sample size should consist of the calculated number of patients, or all implanted devices, whichever is less.

Source(s) of Patient or Device Data: {C2a. Source(s) of Patient or Device Data} The manufacturer should provide a complete description of subject inclusion/exclusion criteria that will be used in selecting subjects for the study. Specifically, describe whether patients who receive "mix and matched" generators/leads not listed in PMA or PMA supplement approval letters to date will be eligible for the study. The protocol should describe how patients will be recruited into their studies from the universe of all patients receiving these devices. At each center, consecutively implanted patients with the manufacturers ICD components should be enrolled in the study, unless the patient refuses to enroll, or a patient is implanted but not followed at the center due to severe geographic difficulties on the part of the patient.

Use of Premarket Cohort: It may be appropriate for a manufacturer to use some or all of the patients included in the premarket cohort for continued data collection for the RPS study. The manufacturer should describe how the premarket cohort represents the general population under actual conditions of use.

Pooling/Grouping: {C2b. Pooling/Grouping} The data for the overall study will be collected at multiple study centers and combined after statistical comparisons have been made to justify data pooling. Comparisons to be made include the following: patient age, gender, indications for use, clinical condition at enrollment, and overall all-cause mortality rate data. The various centers should use a common study protocol, commonly accepted patient criteria, and commonly accepted patient follow-up practices/protocols.

Manufacturers are encouraged to justify grouping the results of different models together. An adequate justification would entail providing scientifically based arguments why various models are expected to perform similarly, as well as documenting actual performance where possible. The following devices could conceivably be grouped together: connector changes to otherwise identical generators, connector or lead length variations to otherwise identical leads, etc.

Data Collection Plan and Forms: {C3. Data Collection Plan and Forms} Include copies of proposed data forms. Due to patient privacy issues related to the use of Social Security Numbers, we recommend that manufacturers assign each patient a company-specific number that would be used on each subsequent follow-up record. The investigator from each participating center should sign an investigator agreement that contains specific requests for in situ device interrogations and explant in the event of patient deaths whenever this is reasonably possible.

Follow-up Plan: {C4. Follow-up Plan} If some enrolled individuals are reportedly lost from the study, strenuous efforts should be made to locate these apparently lost individuals to obtain information regarding their vital and explant status. These efforts could include contacting the physician of record, or using credit bureaus, the Social Security Administration or National Death

Index Databases. If it is discovered that a patient has died, an effort should be made to contact the patient's last physician or the patient's next-of-kin to determine if and why the patient had his ICD explanted prior to his death. If explant from living patients has occurred during the study period, reasonable efforts should be made to obtain and report the clinical reason that resulted in explant. In the protocol, each manufacturer should describe a detailed plan they will follow for data collection, describe how losses to the study will be measured, and explain the steps that will be taken if the apparent losses to follow-up become excessive (i.e., over 40% loss at 3 years) to obtain the information needed to obtain an acceptable final rate of loss.

Data Quality Control: {C5. Data Quality Control} Techniques for anticipating, identifying, and correcting errors should be described.

Length/End of Study: {C6. Length/End of Study} Based on the information already provided by some manufacturers, an active study duration of 5 years from the date of implantation for the last participating patient is adequate for RPS if the manufacturer demonstrates a majority of previous recalls and alerts have occurred within the first 5 years of introduction of new ICD models. Data derived only from the United States should be submitted, but international data is acceptable if data from the United States is unavailable. Due to statistical uncertainties, the active study would terminate once only 25% of implanted devices remain in service, even if 5 years of follow-up for each patient had not been completed.

Analysis Plan: {C7. Proposed Analytical Plan} A survivorship or numerical analysis of all-cause mortality rates, sudden cardiac death rates, perioperative mortality rates, generator complication rates, generator explant rates, lead complication/failure rate, and lead explant rates should be conducted. In calculating life tables, the following conventions for handling cases of withdrawal and loss to follow-up should be followed. The length of observation for withdrawals is the time of implant to the date of last contact. The length of observation for losses to follow-up is the time from implant to the time of loss, if known. If the time of loss is not known, then it should be considered as the midpoint of the interval between the time of the report of loss and the time of the last documented follow-up. A study patient is considered lost to follow-up only after repeated attempts, for up to one year, to locate the patient have been unsuccessful. Numbers of patients who are considered lost to follow-up or withdrawn should be reported in separate columns of the life table. In the interest of obtaining adequate numbers of events in each cell, and for uniformity of life table analysis among manufacturers, an interval of 1 year should be used.

4. Reporting{D1. and D2. Interim and Final Reporting for the Active Study}

Reports to the CDRH would generally be due at study initiation, and every 6 months thereafter until the end of the study when all patients have reached 5 years post-implantation.

The following information should be provided in each report:

a. Number of implanted patients enrolled to date in the active study

b. Summary of the reasons for explant and the number explanted for each reason

c. to n. Summary data regarding the baseline condition of the patient sample and all-cause mortality rates, sudden cardiac death rates, perioperative mortality rates, generator complication rates, generator explant rates, lead complication/failure rates, and lead explant rates.

In the reports, CDRH may require stratification of the results of pooled models by indications for use (e.g., VT, VF, or both), and any other factors that appear to strongly influence the results (e.g., age, gender, baseline clinical condition, etc.).

Appendix E. Mortality Definitions

All mortality data should be provided. Mortality may be presented using the following categories:

a. total mortality
b. non-cardiac death
c. sudden cardiac death
d. non-sudden cardiac death (with or without morbidity post shock)
e. total cardiac mortality

The following mortality definitions are adapted from the NASPE Policy Statement: Standardized Reporting of ICD Patient Outcome [27].

1. **Noncardiac Death** - deaths not classified as cardiac deaths. Furthermore, the following subdivisions of noncardiac death should be enumerated:

2. **Operative Death** - synonymous with surgical mortality and operative mortality, including all patient mortality from the induction of anesthesia through the subsequent 30 days or during the same hospitalization if it is longer than 30 days, or after the hospitalization if clearly related to the implantation of the ICD, such as in the case of infection. Operative death should be calculated for all surgical procedures with the intention to implant an ICD as documented by the patients signature on a consent form or by other written documentation. Operative deaths are to be tabulated as total cardiac deaths with further subcatagorization by the chronology of the terminal events. Operative deaths should also be reported separately in all ICD studies.

3. **Waiting Period Death** - Death which occurs between the time a decision to implant an ICD is made by the implanting physician and patient (not necessarily accompanied by signed consent) until the operative procedure, and are to be included in the analysis of overall risk of ICD therapy. A signed consent form is documentation of this decision, but timing the waiting period from the signing of the consent may underestimate the duration of the true waiting period.

4. **Hardware Related Death** - Death related to device malfunction should be specifically reported. Examples include lead failure, lead dislodgment, and generator failure. Power source depletion due to failure of patients to report for adequate follow-up is not considered as device malfunction.

5. **Nonsudden Cardiac Deaths** - all cardiac deaths not classified as sudden deaths.

6. **Sudden Death** - death within one hour after onset of acute symptoms. Unwitnessed death which is unexpected and without other apparent cause including death during sleep, should be included in the category of sudden death. However, the number of unwitnessed deaths should be provided in any published report.

7. **Total Cardiac Deaths** - all deaths due to cardiac causes. Surgical mortality resulting from implantation of an ICD should be included among total cardiac deaths.

8. Total Mortality - deaths from all causes.(A person in a chronic vegetative state is considered to be alive).

Appendix F. Definitions of Lead-Related Complications and Failures DRAFT

Revision of these criteria for Lead-Related Complications and Failures are under revision by ACC and NASPE.

Present Lead-Related Complications and Failures using the following:

WHEN: The any one of the following condition occurs:

- Conductor Failure
- Dislodgment
- Extracardiac Stimulation
- Insulation Breach
- Lead Impedance less than 200 ohms (describe how impedance was measured)
- Lead Impedance greater than 3000 ohms or beyond the measuring capabilities of the device (describe how impedance was measured)
- Loss of Capture
- Oversensing
- Perforation
- Undersensing/Loss of Sensing

AND: The condition was not:

- Caused by a pulse generator malfunction or
- Corrected by reprogramming of the pulse generator (except for reprogramming of mode or polarity)

THEN: The occurrence should be reported along with the following interventions/interactions in which the lead was:

- Abandoned Electrically
- Abandoned Surgically
- Modified Electrically
- Modified Surgically
- Removed/Explanted (full or partial)
- Tolerated (based on medical judgment)

Definitions of terms

Conductor Failure: Visual, electrical, and/or radiographic evidence of mechanical break within the lead conductor (includes connectors, coils and/or electrodes).

Dislodgment: Radiographic, electrical or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing and/or lead performance.

Extracardiac Stimulation: Clinical observation of inadvertent muscle/nerve stimulation other than cardiac muscle where the pulse generator has been eliminated as a possible reason for the problem.

Implanted Lead: A lead is considered implanted when the surgical incisions are closed.

Insulation Breach: Visual, electrical, or radiographic evidence of a disruption or break in insulation.

Lead Abandoned Electrically: A lead that remains connected to a pulse generator whose function is disabled through reprogramming (e.g., changed from DDD to VVI) in response to a problem with the mechanical or electrical integrity of the lead.

Lead Abandoned Surgically: A lead that is left in situ, with or without capping, detached from the pulse generator, and not used for sensing or pacing.

Lead Modified Electrically: A lead that remains connected to a pulse generator whose function is altered through reprogramming (e.g., changing from bipolar to unipolar) in response to a problem with the mechanical or electrical integrity of the lead.

Lead Modified Surgically: Any mechanical alteration or repositioning of the lead (e.g., replacing a connector).

Loss of Capture: Intermittent or complete failure to stimulate cardiac depolarization at programmed settings delivered outside of the cardiac refractory period.

Oversensing: At programmed settings, the inability to discriminate between extraneous signals, (e.g., T waves, pacemaker stimuli, skeletal muscle potentials and extracardiac electromagnetic interference) and the intended cardiac depolarization.

Perforation: Penetration of the lead tip through the myocardium, clinically -suspected (microperforation), or confirmed **by** chest x-ray, fluoroscopy, echocardiogram, intracardiac electrogram, and/or visually.

Removed/Explanted Lead: Any segment (partial) of a lead or whole lead system that is removed or explanted.

Tolerated (Lead Function): When a physician determines that no corrective action is warranted to remedy a lead related complication or failure.

Undersensing/Loss of Sensing: Intermittent or complete loss of sensing or failure to detect the intended intrinsic cardiac signals (atrial or ventricular) during pacemaker alert period at programmed settings.

Appendix G. Specific Study Design Options

Table 2 contains a number of specific designs for specific indications. The associated study design work sheets (one for the premarket study and one for postmarket study) illustrate the approach to developing these specific suggestions.

Sponsors, panel members and other consultants can help in developing these designs by:

1. defining the ICD changes (Device Description, Indication, and Clinical Claim) sponsors are most likely to propose in the next few years
2. suggesting an appropriate approach to each study (Primary Endpoints, Trial Design, Type of Control, and number and duration of Follow-up requirements)
3. recommending the amount of improvement in each primary endpoint which would be clinically significant (or lack of difference for an equivalence claim)
4. numbers of patients will follow more or less directly from the power calculations, but suggestions as to numbers and types of study centers would be appreciated

Table 1. ICD Application Categories (repeated from page 4)

Clinical Data Required	Technology Issues		
Premarketing	**Novel Design (1)**	**Evolutional (2)**	**Existing (3)**
PreClinical Testing	Bench + Animal	Bench ± Animal	Bench ± Animal
Clinical Study	Large	Medium	Small
Postmarket surveillance	Yes	Probably	Maybe
Type of Application	Original PMA	PMA Supplement	PMA Supplement
Panel Review	Yes	If first	If first
No Premarketing	**Novel Design (4)**	**Evolutional (5)**	**Existing (6)**
PreClinical Testing	Bench ± Animal	Bench	± Bench
Clinical Study	none	none	none
Postmarket surveillance	Yes	Probably	no
Type of Application	PMA Supplement	PMA Supplement	PMA annual report
Panel Review	possibly	no	no

Table 2.1 Top Ten ICD Clinical Trial Design Summaries

Elements included in the table are presented as EXAMPLES ONLY and are not for guidance purposes

#	Category *	Device Description	Indication	Clinical Claim	Preclinical	Primary Endpoints, Criteria change	Trial Design, Type of Control	Num pats, duration follow-up	Postmarket surveillance
1	1	Add new hemo-dynamic sensor function	Patinet with hemo-dynamically significant arrhythmia	Fewer inap-propriate shicks	Bench + Animal	Treatment success, # inappropriate shocks, mortality	ICD + HDD vs. ICD alone RCT	__ x 12 mo	Yes
2	2	Add DDD pacemaker to ICD	Standard ICD + standard DDD	Reduced inappropri-ate therapy for AF	Fnctnality, simulated use, safety	Appropriate treatment of AF	Two parallel groups, RCT	130 (65/gp) x 6 mos	Yes
3	2	Change in lead system	Standard ICD RV	Equivalent to approved ICD	Bench	pulse-width thresholds at nominal voltage	Two parallel groups, RCT	160 (80/gp) x 6 mos	Yes
4	2	Approved ICD with new antitachy pacing	Standard ICD	Equivalent to approved ICD	Bench	Effectiveness rate for spontaneous VT	Two parallel groups, RCT	86 (43/gp) x 3 mos	Yes
5	2	Approved ICD with electrode change	Standard ICD	Equivalent to approved ICD	Bench	Adequate defibrillation threshold @ implant	Two parallel groups, RCT	246 (123/group) at implant	Yes
6	2	Approved ICD with can-as-electrode	Standard ICD	Equivalent to approved ICD	Bench	Effectiveness rate for spontaneous VF	Two parallel groups, RCT	86 (43/gp) x 3 mos	Yes
7	2	Approved ICD and lead system	Standard ICD+ MADIT type	Equivalent to approved ICD	Engineer. equivalent to MADIT	All-cause 2 year mortality	Observational, multicenter	120 pts x 2 years	**Only**
8	2	Change in implant location, e.g., pectoral	Standard ICD	Equivalent survival to approved ICD	Bench	Equivalent survival to approved ICD	Two parallel groups, RCT	246 (123/group) at implant	Yes
9	2	Change in sensing algorithm, e.g., electrogram width	Standard ICD	Equivalent sensitivity to approved ICD	Bench	Equivalent sensitivity for VT detection	Patient is own control	100 patients, 300 events	**Yes**
10	2	Change in sensing or detecting algorithm,	Standard ICD + rejection of SVT/NSR	Equivalent specificity to approved ICD	Bench	Incremental specificity for rejecting SVT/NSR	Patient is own control	20 patients	**Only**

* *Category refers to Table 1; HDD = Hemodynamic detection; RCT = randomized clinical trial, RV = right ventricle, AF = atrial fibrillation, MADIT = Multicenter Automatic Defibrillator Implantation Trial*

Table 2.2 Clinical Trial Design Summaries (ctd)

Elements included in the table are presented as EXAMPLES ONLY and are not for guidance purposes

#	Category *	Device Description	Indication	Clinical Claim	Preclinical	Primary Endpoints, Criteria change	Trial Design, Type of Control	Num pats, duration follow-up	Postmarket surveillance
11	1	Atrial defibrillator	Atrial fibrillation	Superior to medical management	**Bench + Animal**	Survival, 20% better	ICD vs. medical with 6 mo rescue, Concurrent Randomized	150 x 6 mo	**Yes**
12	2	Approved ICD with can-as-electrode	Standard ICD	Equivalent to approved ICD	Bench	Effectiveness rate for induced VT	Two parallel groups, RCT	300 pts (150/gp) x 3 mos	Yes
13	2	ICD with DDD added to VVI pacemaker	Standard ICD + standard DDD	Equivalent to ICD & DDD	Fnctnality, simulated use, safety	Atrial arrhyth discrimination	Pt own control, stability 6, 30, 60 msec	43, 3 mo f/u (enroll 65)	Yes
14	4	DDD-R (or DDD) pacing	Sick sinus syndrome	Improve-ment in CHF patients					
15	1	Atrial ICD + ventricular ICD	AF in patients with VT/VF	Conversion success (AF and VT/VF)					
16	5	Trans-telephonic follow-up	Enhanced patient follow-up	Reduced MD visit rate					
17									
18									
19									
20									

** Category refers to Table 1; QOL = quality of life; RCT = randomized clinical trial; SCD = sudden cardiac death; ATP = antitachy pacing*

Each study (row) in this summary (Table 2), will be supported by one, two, or three work sheets (Preclinical, PMA and RPS).

PMA Clinical Trial Design Work Sheet

ICD Study # 1 June 19, 1996

Regulatory Category:	Category 1, Novel technical issue, Effectiveness and Safety data required, Original PMA
Device Description:	ICD + new hemodynamic detector (HDD) function
Clinical Indication:	Patient experiencing hemodynamically significant SVT / VT / VF
Clinical Claim:	Equivalent sensitivity, fewer inappropriate shocks
Preclinical Studies:	Complete bench testing and appropriate animal studies will be required
Primary Endpoint(s):	Survival (all causes and cardiac) at 6 mos and 1 year, Frequency of inappropriate shocks
Clinical Trial Design:	RCT, ICD vs. ICD + HDD with 6 mo rescue available, prospective randomization
Type of Control:	Concurrent controls, equal number of patients receive ICD and ICD + HDD
Sample size calculation:	
	Effectiveness: $\alpha = 0.05$ (two tailed), $\beta = 0.2$ (power = 0.8)
	Critical difference = 20% worse mortality at 12 mos
	Sample size (equivalence)[1] (0.05, 0.2, 20%) = ___
	Safety: 95% CI adverse event < 2%
	Sample size (safety)[2] (95%, 2%) = 150
Num pats / arm:	___ (total = ___), assuming 10% dropout,
	enroll ___/arm (total = ___)
Follow-up (#, duration):	___ x 6 mo, __ x 1 year
